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Different Obese Phenotypes and Progenitor Endothelial Cell Dysfunction: The Missed Link to Cardiovascular Risk

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Abstract

Obesity has been remained a leading factor of metabolic and cardiovascular (CV) events worldwide. It has suggesting that obesity might effect on CV risk through several metabolic abnormalities including white adipose tissue and adipocytokines' dysfunction, insulin resistance, impaired glucose metabolism and worsening of an endogenous repair system affected endothelial progenitor cells (EPCs). However, there are serious controversies regarding the level and functionality of EPCs in obese, metabolic syndrome, while EPCs dysfunction is considered a powerful risk factor of CV complications. By now, clinically use of EPC dysfunction as biomarker of altered endothelial function with high predictive ability to risk stratification in obese patients appears to be promised. The mini review is discussed differences in EPC between healthy obese and non-healthy people.

Keywords: Obese, Metabolically healthy obese, Cardiovascular risk, Stratification, Endothelial dysfunction, Endothelial progenitor cells

Abbreviations: MHO: Metabolically Healthy Obese; MNHO: Metabolically Non-Healthy Obese; DM: Diabetes Mellitus; EPCs: Endothelial Progenitor Cells.

Introduction

Obesity has been remained a leading factor of metabolic and cardiovascular (CV) complications, including asymptomatic atherosclerosis, vascular calcification, coronary artery disease, peripheral artery disease, hypertension, and stroke [1]. Although obesity has dramatically increased worldwide [2], the impact of various body-size phenotypes in CV risk and CV outcomes is under discussion [3,4]. Based on the adult treatment panel-III (ATP-III) criteria, there is a concept accordingly of which the levels of BMI and other anthropometric parameters, i.e. height, and waist and hip circumferences, might identify plenty accurate overweight/obesity [5]. Consequently, subjects with established obesity and co-existing metabolic abnormalities including dyslipidemia, insulin resistance (IR), increased fasting glucose and impaired glucose tolerance, are referred metabolically non-healthy, whereas obese individuals without these abnormalities might be defined as metabolically healthy [6,7]. Interestingly, there is not strong definition of metabolically healthy obese as a transient age- and ethnic-related phenotype accompanied to some behavioral and environmental factors [8]. However, accordingly the contemporary "fit but fat" concept an absence of follow sings, such as abdominal type of obesity, insulin sensitivity, impaired glucose tolerance, and low level of cardiorespiratory fitness, is considered an acceptable criteria of metabolically healthy obese [9]. In fact, normal weight individuals exhibit a 60% lower risk of CV disease and events compared with both obese patients' cohorts including metabolically healthy and metabolically non-healthy obese [10]. In fact, individuals with different obesity phenotypes appear to be distinguished from healthy volunteers at CV risk, while patients with metabolically non-healthy obese exhibit higher CV risk and diabetes accompanied with higher frequency of unfavorable clinical outcomes including atherosclerosis-related events and stroke when compared with those who refer as metabolically healthy [11]. On the other hand, there is limited evidence regarding that the ischemic stroke rate is probably accompanied to poor metabolic health rather than with overweight or obesity [4]. Whether metabolomics abnormalities would be powerful tool to stratify the patients with different obese phenotypes is not clear [12]. The contemporary "fat-but-fit" hypothesis has issued from that the metabolically healthy obese is a transient state, which may translate into a metabolically active state over time affecting endogenous reparative response especially in the endothelium [13,14]. In this context, progenitor endothelial cell (EPC) dysfunction may play a pivotal role in target organ damage at the different stages of obese and its transformation in various phenotypes and at diabetes development [15]. Probably, clinically use of biomarkers of altered endothelial function for prediction of and risk stratification of obese patients appears to be promised [16].

The mini review is discussed differences in EPC between healthy obese and non-healthy people.

Definition of endothelial progenitor cells

By now, EPCs have defined as cells, which are positively labeled with both hematopoietic stem cells (CD34) and endothelial cell markers, i.e. predominantly vascular endothelial growth factor receptor-2 (VEGFR2), CD31 cumulatively [17]. There are two types of EPCs, which expressing different level of markers (CD144, Flt-1, VEGFR2, and CD45) and ability to colony forming might determine as early EPCs and late outgrowth EPCs. Late outgrowths EPCs produced more nitric oxide, incorporated more into human umbilical vein ECs monolayer, and are able to better form capillary tube than early EPC. However, early EPC secreted more angiogenic cytokines than late EPC at culture. The early EPCs intervened in the monolayer of human umbilical vein endothelial cells (HUVEC), whereas late EPCs were incorporated to HUVEC [17]. Additionally, two types of EPC might have different roles in neovasculogenesis and neovascularization. Outgrowth endothelial progenitors as a subpopulation of EPCs exhibit a protective impact on the endothelium mediating proliferation and having the ability to promote angiogenesis and collateral vessel growth [18]. These processes are under strong paracrine and epigenetic regulation affected in particularly migration, proliferation, and mobilization of EPCs from bone marrow and peripheral tissues [19,20].

Determination of the progenitor endothelial cell dysfunction

The reduced ability of EPCs to realize their potency in proliferation, differentiation, adhesion, migration, incorporation into tubular structures, and survival defined as progenitor cell dysfunction [21]. Therefore, wear EPCs functionality may associate with lowering EPCs' count in the peripheral blood that is considered an initiation of endothelial dysfunction and any cause-related vasculopathy linked etiological factors, co-morbidities, aging and CV events [22,23]. Nevertheless, EPCs dysfunction well predicts CV risk in general population and in subjects with established CV and metabolic disease [24-26].

The primary reason of metabolic states-related deficit of circulating EPCs which has been particularly attributed to their defective mobilization, proliferation and shortened survival is not fully clear. In fact, glucose toxicity, lipid toxicity, inflammation and reactive oxidative species are now recognized as mainly factors contributing in EPC dysfunction in diabetes. They act through decreased expression of protein kinase A regulatory subunit 1β (PRKAR1β), activation of protein kinase A (PKA), matrix metalloproteinase-9, and phosphorylation of α4 integrin on serine 988 [27]. However, an alteration of structure/function and reduced number of circulating EPCs have now identified in prediabetes [23,28]. In contrast, controversial results regarding being of progenitor dysfunction in obese individuals beyond diabetes were found for last decade [29,30]. The first controversial affects the obese children and adolescents, in which circulating EPC count is elevated accompanying to body mass index and evidence of endothelial activation [30]. The next controversy relates to evidence regarding that the adult obese individuals may present an exaggerated number of endothelial cell-originated microparticles, a low number of EPCs, and high levels of adipokines in peripheral blood beyond inflammatory condition [31]. Moreover, in adult obese individuals circulating EPC number may decrease along with elevated serum level of visfatin, insulin resistance and accumulation of oxidative stress product [32]. Else, the heterogeneity of obese population associated with difference in genetic mutations might be a factor to determine the higher variability of the clinical studies 'results regarding biomarkers' use to predict CV outcomes. Indeed, there is evidence that the individual susceptibility for obese-related complications including T2DM could be related to the matrix metalloproteinase 9 gene (*MMP9-1562 T* gene), 59029A polymorphism in chemokine receptor 5 (CCR5) [33,34]. Because *CCR5* and *MMP9* are over-expressed on EPCs after their stimulation and are involved in the mobbing of EPCs, it is suggesting that the several pathogenetic factors in obese might act via genetic and probably epigenetic mechanisms [35]. Although the results are conflicting and inconclusive, there are possibilities to get extension in the genes investigation in future.

Progenitor endothelial cell dysfunction and cardiovascular risk

Because recent studies have found that the deficiency of EPC and their functional alterations tightly associated with the development and progression of CV disease [36,37], dysfunction of EPC may be first early and probably potentially reversible sign of exhaustion of endogenous endothelial reparation mechanisms leading to the development of endothelial dysfunction and asymptomatic vascular damage in obese individuals of various aging.

Interestingly, EPCs isolated from peripheral blood of the patients with known CV diseases and diabetes have exhibited an impaired migratory and weak proliferative response, which have confirmed being of "EPC impaired phenotypes" pre-existing in subjects with CV risk factors prior established CV disease [21]. However, the circulating level of EPCs in patients with established higher CV risk is very variable and does not fully correlate with number of CV risk factors [38].

The weak ability of EPCs to migration and proliferation in obese beyond diabetes and established CV disease is not confirmed absolutely. **Table 1** reported the changes in EPC number and functionality in adult obese persons in comparison to healthy volunteers. Interestingly, children and adolescents with metabolically healthy obese demonstrate activation of the endothelium associated with transitory increased level of the EPC in the peripheral blood.

Consequently, metabolically non-healthy obese frequently accompany to reduced number of EPCs and their functionality.

Table 1 Comparison of EPC number and functionality in obese and diabetes mellitus.

	MHO	MNHO	DM
Number of circulating EPCs	↑	↓	↓↓
Ability to mobilization	↑	↓	↓↓
Ability to proliferation	↑	↓ or ↓↓	↓↓↓
Survival	-	- or ↓	↓↓↓

Note: arrows indicate the changes in EPC number and functionality in adult obese persons in comparison to healthy volunteers. (↑) - Increased number; (↓) - decreased number; (↓↓) - sufficiently decreased number; (↓↓↓) - extremely decreased number; (-) – no changes.

It might be speculated that the different obese phenotypes appears to be distinguished in endothelial activation and that metabolically non-healthy obesity is accompanied to weak EPC functionality and lowering EPC count. However, development of insulin resistance, metabolic syndrome and type 2 diabetes mellitus has closely associated with weak ability of EPCs to mobbing, and the lowered level of circulating EPCs was determined. Whether EPC dysfunction would be early biomarker to determination of asymptomatic vasculopathy in obese beyond diabetes to risk stratification is not completely understood, while this suggestion is obviously promised.

Conclusion

EPC dysfunction is probably powerful factor linking obese, CV events with age by impairing angiogenesis and vascular reparation. Large clinical investigations are required to explain in detail whether progenitor dysfunction is not only whiteness of nature evolution of the obese, but it is factor contributing in transformation of healthy obese to metabolically non-healthy phenotype. Therefore, EPCs might be considered a delivery system to transfer drug(s) to endothelium the in future, while the current results are inconclusive.

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